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(54) INJECTABLE COMPOSITION

(71) We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA (TAKEDA CHEMICAL INDUSTRIES, LTD.), of 27, Doshomachi 2-chome, Higashi-ku, Osaka, Japan, a corporate body organised under the laws of Japan, do hereby declare the invention, for which pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to an oily injectable composition and to the production thereof.

It is well known that such hormones as estradiol divalerate, estradiol cyclopentylpropionate, testosterone propionate, hexestrol dicaprylate and diethylstilbestrol dipropionate have their specific actions on humans and animals. In order to produce the specific effects of the hormones effectively, it is necessary to prepare such hormones in the form of injectable preparations. For the purpose of preparing injections of such hormones, attempts were made, for example, to dissolve such hormones in vegetable oils such as sesame oil, cotton-seed oil, peanut oil and olive oil. However, these vegetable oil solutions of the hormones have so high a viscosity that they cannot be administered parenterally without giving local pain or necrosis to the host. Attempts were made to reduce the local pain by adding benzyl alcohol to the vegetable oil solution of the hormones, but the high viscosity was not reduced to a sufficient degree.

The concentration of the lipophilic hormones in the injectable preparations is usually higher than about 0.5 weight per cent, and is desirably often as high as 5 weight per cent or even up to 10 weight per cent.

Therefore, the solvent, i.e. the injectable vehicle for the lipophilic hormones, is also required to have the capacity to keep the hormones dissolved therein at a desired concentration, at a number of temperatures, e.g. −20° C. to 40°C.

Under such circumstances, attempts have been made to find a suitable vehicle composition for making the hormones satisfactorily injectable.

The present invention provides an oily vehicle composition for injection of the hormones, an oily injectable solution of the hormones which can be satisfactorily administered and methods of preparing the oily vehicle and the oily injectable solution.

The oily vehicle of the present invention is prepared by admixing benzyl benzoate, chlorobutanol and vegetable oil.

The benzyl benzoate is used in an amount of from 10 to 50 weight per cent, especially from 15 to 30 weight per cent, relative to the total weight of the vehicle composition.

The chlorobutanol is used in a proportion of from 0.5 to 5 weight per cent, especially from about 1 to about 3 weight per cent, relative to the vehicle composition.

When the amount of the benzyl benzoate of the present invention is less than 10 weight per cent, the viscosity of the oily vehicle is not sufficiently low to make the resulting solution injectable without harm. When the amount of the chlorobutanol of the present invention is less than about 0.5 weight per cent, the antiseptic effect of the oily vehicle is remarkably reduced. The upper limits of the benzyl benzoate and chlorobutanol of the present invention are provided for practical purpose. On preparing the oily vehicle of the present invention, the respective ingredients may be admixed in any order. The vegetable oil of the present invention is exemplified, by sesame oil, cottonseed oil, peanut oil and olive

[Price 5s. 0d. (25p)]

oil.

The oily vehicle thus prepared is employed for preparing an injectable solution of the hormones of the present invention. The injectable solution of the present invention is prepared by incorporating the hormones into the oily vehicle produced in the manner mentioned above. The respective ingredients constituting the injectable solution of the present invention may be admixed in any order. Of course, the injection solution of the present invention should be prepared under sterile conditions.

The injectable solution of the present invention thus prepared preferably has a viscosity which is such that it is satisfactorily injected without any undesirable effects. Furthermore, the injectable solution of the present invention gives only slight pain upon injection due to the incorporation of chlorobutanol in the solution.

An example of the present invention is now given. Throughout the description and claims, part is on a weight basis unless otherwise stated.

EXAMPLE

2.5 Parts of 4-hydroxy-19-nor-testosterone 17 - cyclopentylpropionate and 2 parts of chlorobutanol are admixed with 20 parts of benzyl benzoate. The resulting mixture is dissolved in a sufficient amount of sterilised pure sesame oil to make the total up to 100 parts. The resulting oil solution is filtered under sterile condition and then filled up into ampules.

As the control, an oily solution is similarly prepared employing 2.5 parts of the same steroid compound as the above and 10 parts of benzyl alcohol.

The viscosity of each of the two kinds of oily solution thus prepared is examined to give the following result when measured by rotary viscometer at 20°C..

Oily solution	Viscosity (centipoises)
The present invention	50
Control	80

An oily injectable vehicle (solvent) is prepared according to the following formulae, and the viscosity of each of the oily solutions is similarly examined to give the results shown below.

Formula:

Chlorobutanol	3 parts
Benzyl benzoate	30 parts
Sterilised pure sesame oil	67 parts

This vehicle is suitable for dissolving 2 parts of hexestrol dicaprylate to give a satisfactorily injectable solution.

The viscosity of the injectable preparation containing 2 parts of hexestrol dicaprylate dissolved in the vehicle composition prepared as above is compared with that of a hitherto-employed preparation which has the following formula:

Hexestrol dicaprylate	2 parts
Benzyl alcohol	3 parts
Sterilised sesame oil	Added to make 100° parts in total.

Oily solution	Viscosity
Oily solution of the formula	40
Control solution of the formula	90

WHAT WE CLAIM IS:—

1. An oily injection vehicle for lipophilic hormone injections, which consists substantially of (a) from 10 to 50 weight per cent of benzyl benzoate, (b) from 0.5 to 5 weight per cent of chlorobutanol and (c) remainder vegetable oil.

2. An injection vehicle according to claim 1, wherein the amount of benzyl benzoate is from 15 to 30 weight per cent.

3. An injection vehicle according to claim 1 or 2, wherein the amount of chlorobutanol is from 1 to 3 weight per cent.

4. An injectable solution which consists substantially of (a) from 10 to 50 weight per cent of benzyl benzoate, (b) from 0.5 to 5 weight per cent of chlorobutanol, (c) lipophilic hormone and (d) remainder vegetable oil, wherein percentages are based on the total weight of the injection vehicle comprising (a), (b) and (d).

5. An injectable solution according to claim 4, wherein the amount of the hormone is from 0.5 to 10 weight per cent, based on the total weight of the injectable solution.

6. An injectable solution according to claim 4 or 5, wherein the hormone is 4-hydroxy-19-nor - testosterone-17 - cyclopentyl propionate.

7. An injectable solution according to claim 4 or 5, wherein the hormone is hexestrol dicaprylate.

8. A method of preparing an oily injection vehicle for lipophilic hormones which comprises admixing (a) from 10 to 50 weight per cent of benzyl benzoate, (b) from 0.5 to 5 weight per cent of chlorobutanol and (c) remainder vegetable oil.

9. A method of preparing an oily injection solution which comprises admixing a lipophilic hormone with the oily injection vehicle claimed in claim 1.

10. A method according to claim 8 or 9, wherein the amount of the benzyl benzoate is from 15 to 30 weight per cent.

11. A method according to any of

claims 8 to 10, wherein the amount of the chlorobutanol is from 1 to 3 weight per cent.

12. A method according to any of claims 8 to 11 wherein the vegetable oil is sesame oil, cotton-seed oil, peanut oil or olive oil.

13. A method according to any of claims 8 to 12, wherein the lipophilic hormone is hexestrol dicaprylate.

14. A method according to any of claims 8 to 12 wherein the lipophilic hormone is 4-hydroxy-19-nor-testosterone-17-cyclopentylpropionate.

15. A method according to any of claims 8 to 14, wherein the amount of the lipophilic hormone is from 0.5 to 10 weight per cent, based on the total weight of the injectable solution.

16. An oily injection vehicle as claimed in claim 1 substantially as herein described with reference to the specific example.

17. An injectable solution as claimed in claim 4 substantially as herein described with reference to the specific example.

18. A method as claimed in claim 8 or 9 substantially as herein described with reference to the specific example.

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